

Peer Review File

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Reviewer A

This manuscript is interesting research regarding the feasibility and safety of utilizing VATS in the management of patients with central-located SqCLC following neoadjuvant chemoimmunotherapy. Authors concluded that VATS for centrally-located SqCLC following neoadjuvant CIT was found to be feasible, with perioperative outcomes comparable to those of thoracotomy. However, there are several crucial issues.

#1 Authors emphasized that all three cases experienced tumor relapsed was standard lobectomy, but not extended lobectomy, using VATS approach, and expressed that careful consideration should be given to the extent of resection to optimize patient long-term outcomes. However, there were no significantly difference between standard lobectomy and extended lobectomy in OS and RFS using VATS. Therefore, it is difficult to explain those discussion.

Reply 1: We express our sincere appreciation to the Reviewer for their thoughtful suggestions. Neoadjuvant chemoimmunotherapy is an emerging treatment strategy in the clinical management of advanced lung cancer. However, the lack of sufficient real-world data with a long follow-up time poses a significant challenge. In this study, the current cohort is hindered by a small sample size and a short follow-up duration, which could substantially reduce the statistical power when comparing standard lobectomy (N=16) and extended lobectomy (N=9) in terms of OS and RFS using VATS.

Interestingly, all three cases experiencing tumor relapse in the VATS-treated group were from the standard lobectomy group rather than the extended lobectomy group. This observation raises questions about whether this is a mere coincidence or if there may be a meaningful pattern. It is essential to pay close attention to these findings in future research. A larger cohort involving multiple centers with long-term follow-up may offer more insights and help address this question definitively.

In the revised manuscript, we restate and tone down the interpretation and conclusion.

Changes in the text: see Page 3, line 54; Page 13-14, line 258, line 275-283; New Figure 3.

#2 Authors should be shown the data of Kaplan meier curve of RFS and OS compared with between standard lobectomy and extended lobectomy in open-surgery group.

Reply 2: We extend our gratitude to the Reviewer for their valuable suggestions.

Within this cohort, there are only 13 cases in the open-surgery group, with 4 undergoing standard lobectomy and 9 undergoing extended lobectomy. The limited sample size poses a challenge when attempting to construct Kaplan-Meier curves for both RFS and OS comparisons between standard lobectomy and extended lobectomy in the open-surgery group. We showed

the data in new **Figure 2D**, as suggested.

Changes in the text: see new **Figure 2D**; Page 12, line 238-247; Page 23, line 433-434.

#3 As shown in Table 1, radiotherapy was included treatment for centrally-located SqCLC in this cohort. Because Radiotherapy may be affected the incidence of recurrence, author should be described the methods and data of radiotherapy treatment in detail.

Reply 3: We thank the Reviewer for their kind suggestions.

The remaining patients receiving adjuvant radiotherapy after tumor relapse Typically, similar preoperative treatment regimens were continued into the postoperative adjuvant phase. In cases where the resection margin was positive (2 cases in this cohort), postoperative adjuvant radiotherapy was administered. Furthermore, patients with pathologically-confirmed lymph node metastasis after surgery or tumor relapse commonly received adjuvant radiotherapy as determined by the multidisciplinary oncology team. We added the details as suggested.

Changes in the text: see Page 9, Methods section, line 174-179.

Reviewer B

This is a retrospective article focusing on patients who underwent surgery for central or locally advanced squamous cell lung carcinoma following chemio-immunotherapy via VATS or open surgery.

Comments on the Format:

The English is generally sound.

In line 80, the presentation of results and conclusions is misplaced.

An "highlight box" is missing.

Reply 1: We thank the Reviewer for their kind suggestions.

We had restated this paragraph as suggested. Also, we had added the "highlight box" in the revised manuscript.

Changes in the text: see Page 4, line 59-66; Page 6, line 96-98.

Comments on the Content:

Methods:

Vital information regarding the definition of central tumors is lacking. What were the specific radiographic criteria employed to classify a tumor as central? What TNM stage patients were included in the study?

Reply 2: We thank the Reviewer for their kind suggestions.

Central lung cancer is defined as lung cancer located in the segment, lobe, or main bronchus, while lung cancer located below the segmental bronchus is defined as peripheral lung cancer. Clinical IIa-IIIb stages were included in this study. We added this information accordingly.

Changes in the text: see Page 6, line 108-109; Page 8, line 147-149; page 13-14, line 284-287; page 20-21, Table 1.

Results:

A flow chart detailing the study's patient selection and inclusion process is missing and would greatly aid in understanding.

The results section contains only one table, and it lacks crucial data. For an article comparing two surgical techniques, there is a notable absence of perioperative and postoperative data, such as the number of lobes removed, lesion sizes, ASA scores, operative duration, intraoperative complexities, and lymph node dissection details.

Nearly 40% of patients in each group received radiotherapy. It remains unclear whether this radiotherapy was postoperative or part of the initial treatment strategy for oligometastatic disease involving metastatic site radiotherapy. This issue ties into the absence of initial disease staging, making it crucial to clarify.

The article should provide information on the duration and type of treatment administered after surgery.

Reply 3: We thank the Reviewer for their kind suggestions.

We added a flow chart as suggested. Also, more detailed information was included in Table 1. The remaining patients receiving adjuvant radiotherapy after tumor relapse Typically, similar preoperative treatment regimens were continued into the postoperative adjuvant phase. In cases where the resection margin was positive (2 cases in this cohort), postoperative adjuvant radiotherapy was administered. Furthermore, patients with pathologically-confirmed lymph node metastasis after surgery or tumor relapse commonly received adjuvant radiotherapy as determined by the multidisciplinary oncology team. As suggested, the information on the duration and type of treatment administered after surgery was also provided in the Methods section.

In Table 1, in our initial submission, we do have some of the perioperative and postoperative data as mentioned by the Reviewer. For example,

- regarding the number of lobes removed, we presented as standard vs. extended lobectomy. Specifically, for the type of extended lobectomy, we list the number of Sleeve (meaning one lobe resection plus bronchial reconstruction), Bilobectomy (meaning two lobes resection), and Pneumonectomy (meaning all lobes resection in one side)
- regarding the lymph node dissection details, we used No. of retrieved LN instead
- regarding the intraoperative complexities, in our results section, we reported one case within the VATS group requiring conversion to thoracotomy due to adhesions

As suggested, we added some more perioperative data, such as lesion sizes (indicated as clinical T stage) and operative duration

Changes in the text: see page 20-21, Table 1; Page 9, Methods section, line 174-179; Page 6, line 106, Page 23, line 422-424, new Figure 1.

Discussion:

It would have been interesting to discuss the patient selection criteria for VATS versus open

surgery and propose an algorithm to guide surgeons in making this choice.

The discussion does not address the potential presence of falsely positive lymph nodes on PET scans during reevaluation after immunotherapy treatment.

Are there PET scan criteria that would preclude surgery?

Reply 4: We thank the Reviewer for their constructive suggestions.

Generally, the selection criteria for choosing between VATS and open surgery primarily depended on the individual preferences of the surgeons, as well as factors such as tumor location assessed through CT scans and bronchoscopy, along with the degree of tumor response. There was no consensus regarding the choice of surgical approach within our institution.

Recently, our team, along with other researchers, has thoroughly investigated and discussed the limited efficacy of PET-CT scans in evaluating lymph node involvement in lung cancer patients undergoing immunotherapy (please see PMID: 36116212, PMID: 34733630, and PMID: 34413300). For lung cancer patients with clinical N0-N2 & M0 stage, those with initial cN2 stage (indicating metastasis to ipsilateral mediastinal lymph nodes) and a reduction in metabolic activity in the affected lymph nodes (N2) following treatment are typically deemed suitable candidates for surgery. Conversely, patients with distant metastases, cN3 stage (indicative of contralateral mediastinal lymph node metastasis), or an increase in metabolic activity post-treatment are generally not considered appropriate candidates for surgical intervention.

We had added more details in the Methods section and Discussion section.

Changes in the text: see page 14, line 287-296.

Overall, while the article presents an intriguing subject, it requires essential improvements in terms of data presentation and completeness. Addressing these concerns will enhance the quality and comprehensibility of the research.